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Exploring conformational equilibria of a heterodimeric ABC transporter by electron paramagnetic resonance

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ABC exporters pump substrates across the membrane by coupling ATP-driven movements of nucleotide binding domains to the transmembrane domains, which switch between inward and outward facing orientations. Understanding their cycle has potential for medical applications because they are involved in multidrug resistance of cancer cells. Site-directed spin labeling electron paramagnetic resonance and the dipolar spectroscopy technique called DEER or PELDOR was used to investigate the conformational transition of the ABC heterodimeric exporter TM287/288 from the hyperthermophile *T. maritima*. The analysis revealed that with nucleotides the transporter exists in an equilibrium between the IF and OF states. ATP binding without hydrolysis was sufficient to partially populate the OF state, and an almost complete conformational shift was observed when nucleotides were trapped in a pre-hydrolytic or post-hydrolytic state. At physiological temperature and without nucleotides, the NBDs disengage asymmetrically while the conformation of the TMDs remains unchanged. Nucleotide binding at the degenerate ATP site prevents complete NBD separation, a molecular feature differentiating heterodimeric ABC exporters from their homodimeric counterparts. Our data suggest hydrolysis-independent partial closure of the NBD dimer, which is further stabilized as the consensus site nucleotide is committed to hydrolysis. A unified mechanism is established, which reconciles the available information for heterodimeric ABC exporters.

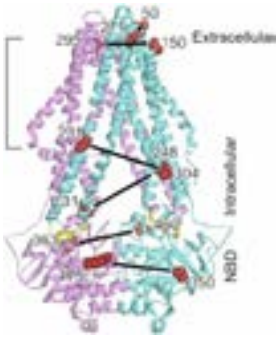

Figure1: *Spin labeling sites in the extracellular, intracellular and NBD regions of TM287/288, represented in the inward-facing apo crystal structure (PDB:4Q4H). TM287 is colored in cyan and TM288 in pink.*

Biography

Enrica Bordignon is an Associate Professor at the Ruhr University of Bochum, where she leads an EPR laboratory dedicated to the study of membrane proteins. She published approximately 50 papers in protein research by EPR methods. Her research interest is understanding the mechanism of action of proteins by EPR.

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